REMARKS

Claims 16-24 were pending prior to the entry of this amendment.

The Amendments

Claim 22 is amended to recite "defined-size droplet particles." Support for the amendment can be found, for example, at page 9, lines 3.

New Claim 25 is, for example, supported by page 6, lines 8-9.

New Claim 26 is, for example, supported by page 9, lines 9-10 and line 19.

New Claim 27 is, for example, supported by page 9, line 5; and page 17, lines 4-5.

New Claim 28 is, for example, supported by page 9, line 5.

All the other claim amendments are to correct antecedent basis or to clarify the meaning of the claims.

No new matter is introduced in any of the amendments.

The Response

35 U.S.C. §103(a) Rejections

1. Claims 16-24 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Huland in view of both Debs and Ruskewicz, and further evidenced by Nayar or Hora. Claim 24 is canceled. The rejection to the remaining claims is overcome in part in view of the claim amendments, and traversed in part.

The Examiner contends that Huland teaches an aerosol composition containing salt, buffer or sugar as well as amino acid or alcohols such as polyethylene glycol. Further, the Examiner asserts that Huland teaches a composition of cytokines including interferon gamma. The Examiner also cites Debs as a reference teaching the use of aerosolized interferon gamma to stimulate alveolar macrophage and blood monocytes. Ruskewicz is relied on for the formation of aerosols of a particle size of 1-12 microns, more preferably 3.0-6.0 microns, by a forced extrusion device. Nayar is cited as a reference teaching serum-free stabilization of proteins, and Hora is cited for teaching stabilization of IL-2 formulation by physiologically compatible stabilizers. Applicants respectfully traverse this rejection.

As currently amended, claim 22 recites an aerosol formulation wherein the aerosol particles are within a defined size range of (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns, and the biological activity and protein molecular size of interferon gamma is substantially the same as those of the aqueous solution. The cited references, either alone or in combination, do not teach or suggest any of the above claimed features.

The Cited References Do Not Teach or Suggest Claimed Particle Size Ranges

Neither Huland nor Debs provides a composition of γ-IFN over the presently claimed defined particle size ranges. Likewise, neither Nayar nor Hora describe an aerosol composition over the presently claimed particle size ranges recited in Claim 22.

At Column 17, lines 58-60, Ruskewicz discloses "an aerosol preferably having a particle size in the range of about 1 to 12 microns, more preferably of about 3.0 to 6.0 microns." However, Ruskewicz does not teach or suggest the claimed particle size range of: (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns. Each of the claimed particle size ranges has a unique application. For example, Applicants have described the desired droplet particle size of less than 1 micron for treating cystic fibrosis, 1-3 micron for delivery to bronchial sites, and 3-5 microns for administering systemically (see application at page 15, lines 1-7).

Neither of the cited references teaches or suggests the claimed particle size ranges, therefore, the combination of the cited references does not produce the claimed defined particle size ranges.

The Cited References Do Not Teach or Suggest Claimed Retention of Substantially the Same Biologic Activity

Claim 22 recites a composition of aerosol droplet particles with an interferon- γ biological activity and molecular size distribution substantially the same as those of the aqueous interferon gamma solution. In the application at page 13, lines 10-17, Applicants describe that:

> In addition to predictability and uniformity in droplet size, it is important that the aerosolization process, which is associated with high local shear forces, does not significantly alter the biological activity or the molecular size distribution of γ-IFN in the aerosol. The two characteristics may be

linked, inasmuch as γ -IFN is active in a dimerized state, and may be expected to lose activity, either by monomerization of aggregation, when subjected to the high shear forces associated with aerosolization, and/or by protein denaturation at the liquid/air interfaces in small aerosol droplets.

None of the cited references Huland, Debs, Ruskewicz, Nayar or Hora describe an aerosol droplet composition of γ-IFN with retention of substantially similar γ-IFN activity in comparison with the liquid composition prior to aerosolization. Huland, Ruskewicz, Nayar or Hora do not measure the biologic activity of IFN- γ. Debs merely describes the immunomodulatory effects of aerosolized rMuIFN- γ on rat alveolar macrophage and blood monocyte function. Debs does not measure the biological activity before and after aerosolization. Debs does not describe that the IFN- γ potency remains substantially the same after aerosolization.

On the contrary, Applicants have demonstrated in Figure 6 that three aerosolized formulations showed substantially the same biological activity as the non-aerosolized solution (see Figure 6 and page 13, line 31 through page 14, line 4).

The Cited References Do Not Teach or Suggest Claimed Retention of Substantially the Same Molecular Size Distribution

None of the cited references Huland, Debs, Ruskewicz, Nayar or Hora describe a composition of γ-IFN with substantially the same molecular size distribution after aerosolization. None of the cited references provide data regarding the molecular size distribution.

On the contrary, Applicants have demonstrated in Figures 7 and 8 that by molecular analysis of the samples, aerosolization of IFN- γ solution has no measurable effect on the molecular size distribution, i.e., the state of dimerization or aggregation of the IFN- γ (see Figures 7 and 8 and page 14, lines 21-25).

Accordingly, for at least the foregoing reasons, Applicants submit that claims 16-23 are patentable over the cited references, either alone or in any combination. Withdrawal of the rejection is respectfully requested.

2. Claims 16-24 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Huland and Jaffe in view of both Debs and Ruskewicz as further evidenced by Nayar or Hora.

Claim 24 is canceled. The rejection to the remaining claims is overcome in part in view of the claim amendments, and traversed in part.

As discussed above, Huland, Debs, Ruskewicz, Nayar, and Hora do not render Claims 16-23 obvious. The addition of Jaffe does not cure the deficiency of other references.

Jaffe describes a formulation with a particle size of "0.1-3 μm mass median diameter (50% of droplets less than or equal to 0.1-3 μm)" (see page 297, right column, first full paragraph). Jaffe does not teach or suggest the claimed particle size of: (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns.

Although Jaffe disclose that rIFN-γ can be aerosolized and inhaled and retain some biologic activity after reaching the lower respiratory tract, Jaffe does not show that the biological activity of the aerosolized γ-IFN is substantially the same as that of the aqueous γ-IFN solution. Further, Jaffe does not show that the molecular size distribution of the aerosolized γ-IFN is substantially the same as that of the aqueous γ-IFN solution.

Accordingly, Applicants respectfully submit that the 35 U.S.C. 103(a) rejection of Claims 16-23 over Huland and Jaffe in view of Debs, Ruskewicz, Nayar and Hora should be withdrawn.

35 U.S.C. §112, First Paragraph Rejection

Claims 22 and 24 are rejected under 35 USC 112, first paragraph as failing to comply with the written description requirement. Claim 24 is canceled.

The Examiner contends that the original claims did not specify the stabilizing agent and the dispersing agents used in the instant invention. The Examiner further contends that while the specification discloses stabilizing agents such as sugar, alcohol, and amino acids, it does not describe the combination of these agents. The Examiner also contends that neither the claims nor the specification disclose a preparation excluding serum albumin.

In response to the Examiner's new matter rejection, Applicants have amended Claim 22 to the claim to recite that stabilizing agents consists of a sugar, an alcohol or an amino acid, and have deleted language referring to a combination. Applicants have further amended the claim to remove language directed to a serum albumin-free composition. Accordingly, Applicants submit that the Examiner's rejection is rendered moot by the present claim amendment and respectfully request the withdrawal of the rejection.

CONCLUSION

Applicants believe that the application is now in good and proper condition for allowance. Early notification of allowance is earnestly solicited.

Respectfully submitted,

Date: October 6, 2005

Viola T. Kung (Reg. No. 41,131)

HOWREY SIMON ARNOLD & WHITE, LLP
2941 Fairview Park Drive, Box 7
Falls Church, VA 22042
Telephone: (650) 463-8181